35 U.S.C. §112, first paragraph

The Examiner has rejected claims 8 and 16 under 35 U.S.C. §112, first paragraph. The Examiner states that the specification and originally filed claims do not recite a media composition comprising IL-6. Applicants respectfully disagree. The specification discloses a ".....cell expansion media comprising cell growth media, autologous serum, and flt3-L alone or in combination with a cytokine from the group listed above." (page 5, lines 26-28), and in the preceding paragraph on the same page at line 20, the specification includes IL-6 in the list of cytokines. As such, the specification fully supports claims 8 and 16 and the rejection under 35 U.S.C. §112, first paragraph may be properly withdrawn.

Claims 1-8, 17-26, 29 and 30 have been rejected under 35 U.S.C. §112, first paragraph. The heart of the matter lies in Applicants claiming a hematopoietic cell expansion medium comprising flt3-ligand and flt3-ligand variants that are 80% identical to amino acids 28-160 of SEQ ID NO:6. The Examiner is of the opinion that the specification does not meet the written description and enablement requirements to support the pending claims. Applicants respectfully disagree particularly in light of the above amendments and following remarks.

Applicants note that the U.S.P.T.O.'s Written Description Guidelines permit claiming variants using the "at least X %" language so long as the variants (i.e., species within the genus) possess the specified function. Applicants invite the Examiner to review *Example 14: Product by Function* section of the U.S.P.T.O.'s Written Description Guidelines (a copy is included with this response for the Examiner's convenience), taking into account the following arguments.

Applicants have satisfied the written description requirements for the following reasons:

(1) In the application as originally filed, Applicants disclose that the genus of flt3-ligand polypeptides bind flt3 receptor, and in particular, the species having SEQ ID NO:6 and SEQ ID NO:2, as well as fragments and variants thereof, are able to bind flt3 receptor. Applicants further disclose that this functional activity is essential to the operation of the claimed invention. (See for example, page 7, line 33, which states the biological activity of flt3-ligand is mediated by binding to flt3 receptor, and alternatively is capable of transducing a stimulatory signal to the cell). Therefore, the specification and claims teach that the functional attribute of binding flt3 is shared by members of the genus.

(2) The specification defines the genus of flt3-ligand molecules at page 7, lines 18-31. This definition includes the capacity to bind to the flt3 receptor. Flt3-ligand variants are defined as polypeptides that are substantially homologous to a native flt3-ligand, but which have an amino acid sequence different from that of native flt3-ligand (human, murine or other mammalian species) because of one or more deletions, insertions or substitutions (page 8, lines 5-8). Notably, the specification states at page 8, lines 8-9 that the variant amino acid sequence preferably *is at least 80% identical* to a native flt3-ligand amino acid sequence.

(3) Applicants' specification teaches procedures for making biologically active variants at page 8, line 5, *et seq.*, as well as in Examples 3 and 4 (beginning at page 29). Also, the specification teaches isolating additional variants by techniques such as cross-species hybridization techniques (see Example 4 at page 34). Moreover, additional procedures for making variants that have at least 80% identity and retain biological activity are conventional in the art.

(4) The application teaches several assays that may be used to identify flt3-ligand variants having biological activity, i.e., binding to flt3. (See page 16, line 26 to page 19, line 2 for various flt3 binding assays, as well as Examples 10 and 11 for biological function assays).

(5) Applicants have actually reduced to practice two disclosed species (human and mouse flt3-ligand) and that these species share functional activity, i.e., binding flt3 receptor. The two disclosed species are representative of the genus because they possess the required biological activity. Furthermore, Applicants have provided several methods of identifying all of the at least 80% identical variants of SEQ ID NO:6 that are biologically active (see item 4 above).

As such, Applicants respectfully submit that every element of the written description requirements analyzed in Example 14 of the U.S.P.T.O.'s Guidelines have been met by Applicants' disclosure. In light of the above analysis, Applicants respectfully submit that the written description requirements of 35 USC 112 have been fully satisfied for the presently claimed invention.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with what is known in the art* without undue experimentation. Applicants note that a patent need not teach, *and preferably omits*, what is well known in the art *(In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d1331, 1332 (Fed. Cir. 1991)). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (*In re Angstadt*, 537 F.2d 498,504, 190 USPQ 214, 219 (CCPA 1976)). As to what constitutes undue experimentation, a factual

determination of the factors described by the *Wands* Court (see, MPEP 2164.01(a)) is to be performed. Applicants note that the test of whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is allowed if it is routine (*In re Angestadt and Griffin*, 190 USPQ 214; CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 227 USPQ 4528; CAFC 1985). In short, Applicants submit that one of skill in the art would not have to undertake undue experimentation to make and use the claimed invention because determining flt3-ligand polypeptides that are at least 80% identical to SEQ ID NO:6 is considered routine in the art and therefore would not constitute undue experimentation.

Applicants define flt3-ligand at page 7 lines 18-31 in terms of polynucleotide and polypeptide sequences from two species that have been reduced to practice (i.e., SEQ ID NOs:2 and 6). Working examples are provided in Examples 1-5. Notably, a key element in determining enablement is whether the starting materials to make the invention are available. This element has been satisfied by disclosure of mouse and human flt3-ligand polynucleotide and polypeptide sequences in the application as originally filed, as well as deposition of flt3-ligand expression vectors with the ATCC. Applicants note that the specification provides direction to one of skill in the art in making flt3-ligand variants that bind flt3 receptor. The specification provides guidance as to which amino acids may be substituted, deleted or inserted, for example, "Variants may comprise conservatively substituted sequences, meaning that a given amino acid residue is replaced by a residue having similar physiochemical characteristics" (page 8, lines 25-27), and, "Examples of conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example substitutions of entire regions having similar hydrophobicity characteristics, are well known." (page 8, lines 24-28).

A key factor in this analysis is that the claimed invention is qualified by a functional limitation, i.e. flt3-ligand binding to flt3 receptor. Applicants emphasize that the specification teaches one of skill in the art numerous screening assays by which one may identify functional flt3-ligand variants. See page 16, line 26 to page 19, line 2 for various flt3 binding assays, as well as working examples 10 and 11 for biological function assays. Assays of this sort, especially competitive binding assays, were routinely performed at the

time the application was filed and were amenable to large scale screening formats and automation.

Given that the state of the art and the level of ordinary skill are quite high, and that the nature of the invention is such that this type of experimentation is routine, Applicants firmly believe that one of skill in the art would be able to make and use the presently claimed invention using Applicants' original disclosure without undue experimentation. As such, Applicants respectfully request the rejection under 35 U.S.C. be properly withdrawn.

Applicants wish to draw the Examiner's attention to parent application U.S. Patent No. 5,554,512 in which claims of similar scope (i.e., flt3-ligand polypeptides having 80% identity) **have been issued** (a copy is included for the Examiner's convenience). Applicants are at a loss as to why claims in the present application are deemed unpatentable when claims of similar scope have been allowed. Without belaboring the point, all applicants for patents should be entitled to rely on some degree of continuity and consistency in examination.

If the rejection under 35 USC 112, first paragraph is maintained, Applicants respectfully request that the Examiner provide reasons or evidence indicating why the testing of proteins for the ability to bind flt3 would require undue experimentation, and why the present claims are unpatentable in light of U.S. Patent No. 5,554,512.

35 U.S.C. §112, second paragraph

Claims 1, 3-9, 11-18 and 27-30 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner considers claims 1 and 3-8 vague and indefinite by the phrase "A hematopoietic cell expansion media" because the Examiner is unsure whether Applicants are claiming one medium in using the singular "A", or if more than one medium is being claimed. In addition, the Examiner considers the phrase "cell growth media" unclear for similar reasons. While Applicants do not acquiesce to the Examiner's characterization, in order to expedite prosecution the claims have been amended to specify a hematopoietic *medium* and a cell growth *medium*. Thus, the rejection under 35 U.S.C. §112, second paragraph may be properly withdrawn.

Applicants note that Federal Circuit "has repeatedly emphasized that an indefinite article "a" and "an" in patent parlance carries the meaning of "one or more" in open-ended claims containing the transitional phrase "comprising," and "[u]nder this conventional rule, the claim limitation "a," without more, requires at least one." *KCJ Corp. v. Kinetic Concepts*

Inc., 55 USPQ2d 1835 (CAFC 2000). In addition, Applicants note that the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). Applicants mention this to make it absolutely clear that all suitable cell growth media known in the art at the time the application was filed may be used in the claimed composition and methods.

The Examiner has rejected claims 1 and 2 as being vague and indefinite by the abbreviation "flt3-L." In response, Applicants have amended claims 1 and 2 to replace "flt3-L" with "flt3-ligand."

Claims 9 and 11-16 stand rejected as being vague and indefinite for the phrase "comprising a recombinant human flt3-ligand." In response, Applicants have amended claims 9-16 to specify that the flt3-ligand is further defined as comprising recombinant human flt3-ligand.

Lastly, the Examiner has rejected claims 19 and 20 as vague and indefinite by the phrase "wherein the flt3-ligand" where there is no "flt3-ligand" recited in the claims upon which the claims depend. In response, Applicants have amended claims 1 and 2 to provide proper antecedent basis for "flt3-ligand."

35 U.S.C. §102(a) and §103(a)

Claims 1, 2, 5, 17 and 18 stand rejected under 35 U.S.C. §102(a) as being anticipated by *Lyman et al.* Claims 1, 2, 4, 7, 17 and 18 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Lyman et al.* in view of *Gillis et al.* Claims 1-4, 8, 17 and 18 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Lyman et al.* in view of *Heimfeld et al.* Claims 1, 2, 4, 6, 17 and 18 are rejected under 35 U.S.C. §103(a) as being unpatentable over *Lyman et al.* in view of *Palsson et al.*

As suggested by the Examiner, Applicants respectfully submit an executed Declaration under 37 C.F.R. 1.132 by the inventors Stewart D. Lyman and M. Patricia Beckmann to show the reference invention is not by "another." Consequently, the rejections under 35 U.S.C. §102(a) and §103(a) are rendered moot and may be properly withdrawn.

Double Patenting

Claims 1-18, 27 and 29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9 and 10 of copending Application No. 08/399,404. The Examiner has acknowledged Applicants'

request that the rejection be held in abeyance until the finding of allowable subject matter has been determined.

In addition, claims 2, 18 and 28 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,843,423. Applicants have amended claim 2 to specify that the method is an *in vitro* method for expanding hematopoietic cells. As a result, the presently claimed invention is patentably distinct over claims 1-17 of U.S. Patent No. 5,843,423, which pertain to *in vivo* methods. Applicants respectfully request the obviousness-type double patenting rejection be properly withdrawn.

Reconsideration and allowance of the pending claims is kindly requested.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Date: Oct. 23, 2001 Signed: Nanci M. Kertson
Nanci M. Kertson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Stewart D. Lyman and M. Patricia Beckmann
Serial No: 08/994,468
Filed: December 19, 1997
CPA Filed: May 26, 2000

Docket No.: 2813-L
Group Art Unit: 1633
Examiner: J. Kerr

For: MEDIUM CONTAINING FLT3 LIGAND FOR CULTURING HEMATOPOIETIC CELLS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

The following claims have been amended as follows:

1. (Twice Amended) A hematopoietic cell expansion medium~~media~~ comprising a cell growth ~~media~~medium and ~~flt3-L~~flt3-ligand, wherein the ~~flt3-L~~flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

2. (Three Times Amended) An *in vitro* method for expanding hematopoietic cells comprising contacting the cells with ~~flt3-L~~flt3-ligand, wherein the ~~flt3-L~~flt3-ligand binds flt3 and is in an amount sufficient to cause expansion of the hematopoietic cells.

3. (Amended) A hematopoietic cell expansion ~~media~~medium comprising a cell growth ~~media~~medium, flt3-ligand and G-CSF, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

4. (Amended) A hematopoietic cell expansion ~~media~~medium comprising cell growth ~~media~~medium, flt3-ligand and GM-CSF, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

5. (Amended) A hematopoietic cell expansion ~~media~~medium comprising cell growth ~~media~~medium, flt3-ligand and SF, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

6. (Amended) A hematopoietic cell expansion ~~media~~medium comprising cell growth ~~media~~medium, flt3-ligand and EPO, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

7. (Amended) A hematopoietic cell expansion ~~media~~medium comprising cell growth ~~media~~medium, flt3-ligand and a GM-CSF/IL-3 fusion protein, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

8. (Amended) A hematopoietic cell expansion ~~media~~medium comprising cell growth ~~media~~medium, flt3-ligand and IL-6, wherein the flt3-ligand binds flt3 and is in an amount sufficient to cause hematopoietic cell expansion.

9. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 1, ~~comprising~~wherein flt3-ligand comprises ~~a~~ recombinant human flt3-ligand.

10. (Amended) The method of claim 2, wherein the ~~flt3-L~~flt3-ligand ~~is a~~comprises recombinant human flt3-ligand.

11. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 3, ~~comprising a~~ wherein the flt3-ligand comprises recombinant human flt3-ligand.

12. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 4, comprising a recombinant human flt3-ligand.

13. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 5, wherein the flt3-ligand comprises ~~comprising a~~ recombinant human flt3-ligand.

14. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 6, wherein the flt3-ligand comprises ~~comprising a~~ recombinant human flt3-ligand.

15. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 7, wherein the flt3-ligand comprises ~~comprising a~~ recombinant human flt3-ligand.

16. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 8, wherein the flt3-ligand comprises ~~comprising a~~ recombinant human flt3-ligand.

17. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 1, further comprising a cellular growth factor. ~~in an amount sufficient to cause hematopoietic cell expansion.~~

18. (Amended) The method of claim 2, wherein the cells are further contacted with a cellular growth factor. ~~in an amount sufficient to cause hematopoietic cell expansion.~~

19. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 1, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

20. (Amended) The method of claim 2, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

21. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 3, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

22. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 4, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of

binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

23. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 5, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

24. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 6, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

25. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 7, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

26. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 8, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.—

27. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 17, wherein the flt3-ligand ~~is a~~comprises recombinant human flt3-ligand.

28. (Amended) The method of claim 18, wherein the flt3-ligand ~~is a~~comprises recombinant human flt3-ligand.

29. (Amended) The hematopoietic cell expansion ~~media~~medium of claim 17, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

30. (Amended) The method of claim 18, wherein the flt3-ligand is selected from the group consisting of a soluble polypeptide comprising amino acids 28-160 of SEQ ID NO:6 and a soluble polypeptide capable of binding flt3 that comprises an amino acid sequence that is at least 80% identical to the amino acids 28-160 of SEQ ID NO:6.

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